Microvascular protection during cardiopulmonary bypass

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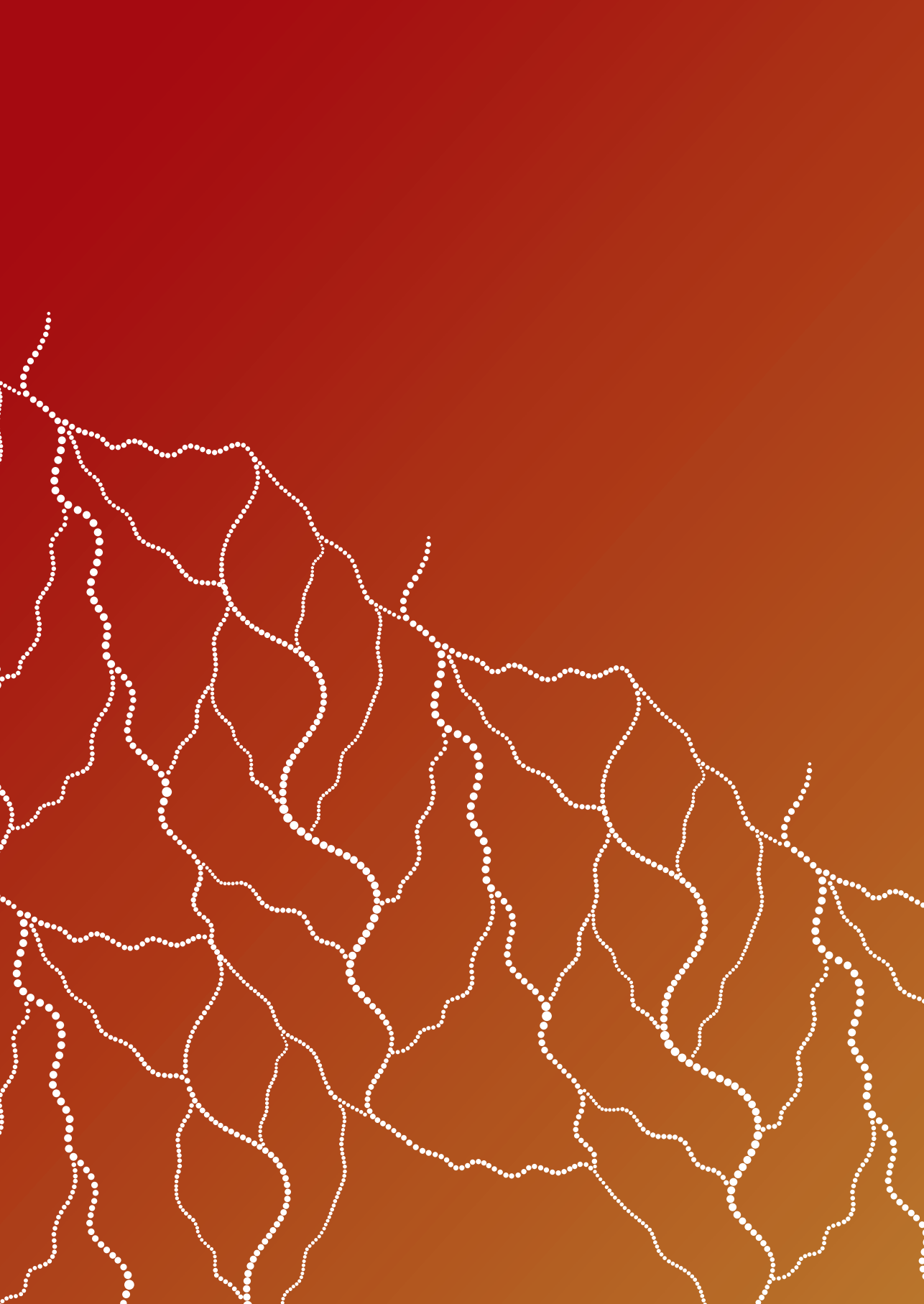

PART II

REDUCTION OF MICROVASCULAR LEAKAGE TO PROTECT MICROCIRCULATORY PERFUSION FOLLOWING CARDIOPULMONARY BYPASS

Chapter 6

Pharmacological interventions to reduce edema following cardiopulmonary bypass: a systematic review and meta-analysis

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ABSTRACT

PURPOSE

To compare the effectiveness of different types of pharmacological agents to reduce organ specific edema following cardiopulmonary bypass (CPB).

METHODS

Pubmed, Embase.com and Cochrane were searched for studies administrating a pharmacological agent before CPB. Primary outcome was postoperative edema.

RESULTS

Forty-four studies (clinical *n* = 6, preclinical *n* = 38) fulfilled eligibility criteria. Steroids were used in most clinical studies (n = 5, 83%) and reduced postoperative edema in 4 studies, however heterogeneity precluded meta-analysis. In preclinical studies, a total of 31 different drugs were tested of which 20 (65%) reduced edema in at least one organ. Particularly neutrophil inhibitors, and modulators of coagulation or endothelial barrier reduced pulmonary edema (SMD -2.77 [-3.93, -1.61]; -1.29 [-2.12, -0.46], -2.33 [-4.69, 0.03], respectively) compared to no treatment. Reducing renal (SMD -0.91 [CI -1.65 to -0.18]), intestinal (SMD -1.98 [CI -3.92 to -0.04]) or myocardial (SMD -1.95 [CI -3.91 to -0.01]) edema following CPB required specific modulators of endothelial barrier.

CONCLUSION

Overall, neutrophil inhibitors and direct modulators of endothelial barrier (PAR1, Tie2 signaling) most effectively reduced edema following CPB, in particular pulmonary edema. Future research should focus on a combination of these strategies to reduce edema and assess the effect on organ function and outcome following CPB.

INTRODUCTION

Edema is a frequently observed complication following cardiac surgery with cardiopulmonary bypass (CPB) that adversely affects postoperative organ function by impairing tissue perfusion.[1-4] The pathophysiology of postoperative edema is however complex and not well understood[1-5], and it therefore remains unclear what pharmacological interventions may effectively prevent this complication.

The vascular endothelium holds a central position in the regulation of fluid transport due to its strategic location between the blood and tissues.[6] Endothelial permeability is tightly regulated and dynamically adapted in response to local needs, such as host defense or altered tissue metabolism. Exposure to an extracorporeal circuit severely alters fluid homeostasis as a result of hypothermia, hemodilution, contact activation, and subsequent transition of the vascular endothelium to a leakier phenotype.[1,6] This increase in vascular permeability results, among others, from the contact of blood components to the non-endothelial surface of the CPB circuit, thereby activating the complement system and initiating a systemic inflammatory response, leading to generalized edema.[1,5] Several types of pharmacological agents to attenuate inflammatory activation or to strengthen the vascular endothelial barrier have been studied in the past years. Nevertheless, their overall effect on organ-specific edema has not been compared and evaluated so far.

Hence, the aim of this systematic review was to provide an overview of available clinical and preclinical evidence on pharmacological agents to reduce edema following CPB, assess the effectiveness of described pharmacological agents on organ specific edema, and identify the potentially most promising pharmacological strategies for further research.

METHODS

PROTOCOL AND REGISTRATION

The protocol for this systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018108433).[7] Systematic review methodology is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[8]

ELIGIBILITY CRITERIA

This systematic review included clinical studies using CPB and studies that utilized animal models of CPB (any species, strain, sex, age and weight). Any protocol of CPB was included (hypothermic, mild hypothermia, pulsatile, non-pulsatile) as well as any duration of CPB. Study protocols with any type of cardiac surgery were eligible for inclusion, but emergency operation, re-operation, pediatric or neonatal subjects, or *in vitro* or *in silico* studies were excluded. As age ranges are not always clearly reported in animal studies, only neonatal animal studies were excluded. Studies administrating a pharmacological agent before onset of CPB were eligible for inclusion, irrespective of dose, timing of administration before CPB, frequency of administration or route of administration. The control population consisted of patients or animals undergoing CPB alone or after administration of a vehicle. The outcomes of interest were parameters representing edema, such as vascular leakage, weight gain, water content, permeability, organ wet-to-dry ratio or glycocalyx thickness.

INFORMATION SOURCES AND SEARCH

Studies were identified for potentially relevant studies by searching Pubmed, Embase.com and Wiley/Cochrane library electronic databases from inception, in collaboration with a medical information specialist. The search strategy was applied to Pubmed, and adapted to Embase and Cochrane (details, see Supplemental Methods). The full search strategy was based on a combination of the following search components (including synonyms and closely related words): 'cardiopulmonary bypass' or 'heart bypass' and 'leakage', 'edema', 'permeability', 'barrier', 'capillary fragility', or 'glycocalyx', as index terms or free-text words. We screened the reference lists of all included studies for additional eligible studies not retrieved by our search. All study designs were eligible for inclusion, but reviews, case reports, meeting abstracts, conference reports, letters or editorials were excluded. The first search was run on 15 August 2018. The search was re-run on 19 March 2019 before final analysis to

retrieve most recent studies for inclusion. No publication date or publication status restrictions were imposed. Non-English studies were excluded during the screening.

STUDY SELECTION

Titles and abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two reviewers (ND and AL). Subsequently, the full text version of these potentially eligible studies was retrieved and independently assessed for eligibility by two reviewers (ND and AL). Discrepancies between reviewers were resolved by consensus and disagreements were discussed with a third reviewer (CvdB), if necessary.

DATA EXTRACTION

Data extraction was performed by one reviewer (ND) and confirmed by another (AL). Data were extracted with regards to study characteristics and design (author, year, type of study, hypothesis), animal model (species, age, experimental groups, size, weight) or patient population (age, sex, groups, weight, cardiac procedure), number of animals or patients, and CPB protocol (technique, type, duration, target flow, aortic cross clamping, normo- or hypothermia). Details regarding interventions (type, timing, concentration, route and frequency of administration, control treatment) and outcome (technique, follow-up time and organ) were also extracted.

QUALITY ASSESSMENT

Quality assessment was performed by two independent reviewers (ND and AL) based on National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) criteria for the quality assessment of controlled intervention studies for clinical studies.[9] The NIH quality assessment tool assess randomization, treatment allocation, blinding, and selective outcome reporting specifically for controlled human intervention studies. "Good", "Fair" or "Poor" was used to indicate the overall quality rating.

For preclinical studies, the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Risk of Bias tool was used to assess methodological quality.[10] The SYRCLE Risk of Bias tool assesses selection, performance, detection, attrition and reporting bias specifically for animal studies and is based on the Cochrane Collaboration Risk of Bias tool. Risks of bias scoring was supplemented with a tenth signaling question focusing on whether the drug was tested in a sham group, an eleventh question focusing on whether a power calculation was performed, and a twelfth question on whether ethical approval was obtained. "Yes", "no" or "unclear"

was used to indicate a low, high or unclear risk of bias, respectively. Based on the risk assessment tools, a final statement was formulated based on whether randomization and blinding were performed at any time point during the study. We assessed the possibility of publication bias by evaluating a funnel plot of the trial standardized mean differences for asymmetry.

STATISTICAL ANALYSIS

The primary outcome was defined as edema following CPB. Studies reporting edema quantified as organ wet-to-dry weight ratio or percentage of tissue water content were used for final quantitative analysis. For studies that only reported tissue water content data, mean and standard deviation of wet-to-dry weight ratios were derived from the mean, standard deviation, and 95% confidence intervals reported for the tissue water content. The meta-analysis was performed for wet-to-dry weight ratio or tracer leakage as primary outcome. Quantitative analyses were performed per organ to correct for potential organ-specific vulnerability to CPB-induced edema formation and potential organ specific responses of interventions. Moreover, pooled analysis were performed when interventions showed comparable mechanisms of action or targeted comparable signaling pathways. Heterogeneity of results was assessed using the I2 statistic. Fixed effects models were used if there was moderate or low heterogeneity (I2 < 50%) and random-effects models were used when substantial heterogeneity (I2 > 50%) was detected. Analysis was performed using Review Manager 5.3 (Cochrane Centre, The Cochrane Collaboration). Meta-analyses were performed if at least two independent studies quantified a similar outcome measure of vascular leakage. If the data were sparse, we reported a narrative synthesis describing the observed effect of studied treatment on postoperative edema.

RESULTS

STUDY SELECTION

The search strategy is presented in a PRISMA diagram (Figure 1 and PRISMA checklist as supplement 1). We identified 2595 records in the primary search and 67 new records were found when the search was repeated. After removal of duplicates (*n*=874), 1817 records were screened, from which 86 full texts were subsequently examined for eligibility. An additional 29 records were identified through snowball searching. Finally, 6 clinical studies and 38 preclinical studies were included. The articles were published between 1981 and 2018 by 38 individual authors and research was performed in 13 countries.

CLINICAL STUDY CHARACTERISTICS AND CPB PROTOCOLS

Patient characteristics and procedural details of included clinical studies are summarized in Table 1. Sample size ranged from 16 to 40 patients. All studies included both sexes and age ranged between 47 to 74 years. One study[11] did not report age range of included patients. Four studies[11-14] (67%) included only isolated

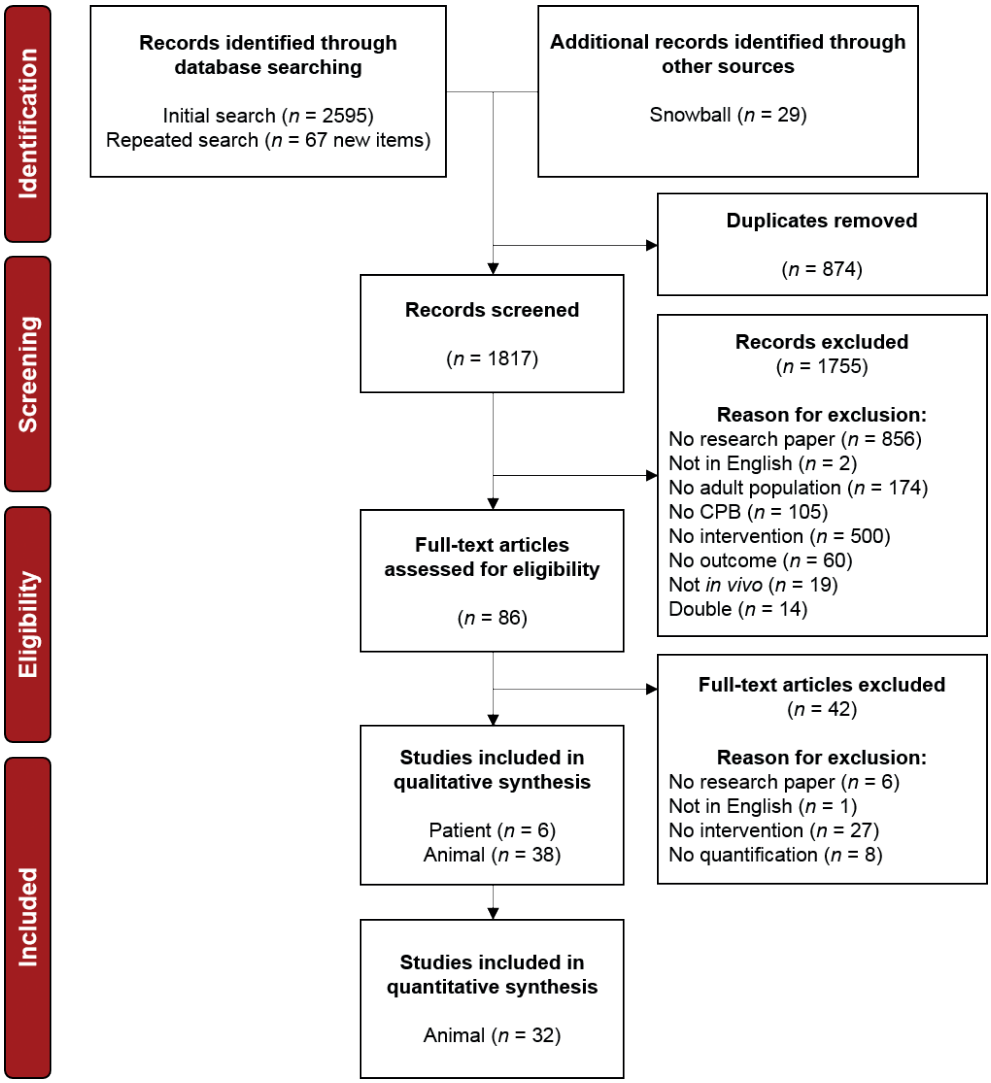

Figure 1. PRISMA flow diagram representing the flowchart of the study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

coronary artery bypass grafting (CABG) surgery, whereas two studies[15,16] (33%) did not report type of cardiac procedural inclusion. All studies used non-pulsatile CPB. On-pump time ranged from 53 to 142 minutes with target temperatures between 28 to 34 degrees during CPB. Follow-up time after weaning from CPB ranged from 0 minutes to 24 hours.

PRECLINICAL STUDY CHARACTERISTICS AND CPB PROTOCOLS

An overview of animal characteristics of preclinical studies is presented in Table 2. Studies were performed in 6 different species. Most studies[17-35] (50%) did not report the sex of the animals, whereas 7 studies[36-42] (18%) used only males, one study[43] (3%) used only females, and 11 studies[44-54] (29%) explicitly stated the use of both sexes. Group sizes varied from 3 to 26 animals per group with a weight range between 240 grams and 67 kilo grams.

Details of CPB protocols are presented in Table 2. None of the animal studies used pulsatile flow during CPB. Large differences were found in type of priming solutions varying from crystalloids[19,20,32-34,37,42-47,49,50,52] (40%), colloids[36,38-41,54] (16%), donor blood[18,51] (5%) or a combination of donor blood and crystalloids[17,21,22,24,30,31,48] (18%). Eight studies[23,25-29,35,53] (21%) did not describe type of used priming solution. On-pump time ranged from 1 to 4 hours with a follow-up time after weaning from CPB from 0 minutes to 7 days.

QUALITY ASSESSMENT

The quality assessment was rated as "poor" for clinical studies and the risk of bias was rated as "high" for preclinical studies. Individual results per study (Supplement 2 - Table 1 and Supplement 3 - Table 2) and a summary of the results is provided as supplement (Supplement 4 - Figure 1 and Supplement 5 - Figure 2). The majority of studies were at risk of selection bias and performance bias due to the lack of reporting of randomization, allocation concealment and blinding. Only 3 clinical studies (50%) and 6 animal studies (16%) used both randomization and blinding at any time point during the study period. There was a potential risk of publication bias, as the funnel plot of pulmonary wet-dry-weight ratio data revealed asymmetry (Supplement 6 - Figure 3). Limited data per outcome measure in combination with large variation in types of therapeutic agents used, hampered such analysis for other organs.

Table 1. Characteristics and cardiopulmonary bypass protocols of included clinical studies

Study and year (Ref)	Country	Patients (number)	Male (%)	Age (years)	Body Weight (kg)	Procedure (type)	Duration procedure (minutes)	Cross clamp time (minutes)	CPB time (minutes)
Brettner 2018 (15)	Germany	30	ND	64 (57 - 74)	82 (62 - 111)	cardiac surgery	NR	control: 79.5 (59.8 - 90.3) interv: 75.5 (39.0 - 94.8)	control: 109 (76.8 - 135.3) interv: 105.5 (61.5 - 121.0)
Miranda 1982 (12)	Netherlands	40	92	51 (47 - 63)	75 (67 - 83)	isolated CABG	control: 390 ± 80 interv: 360 ± 69	control: 79 ± 8 interv: 75 ± 20	control: 180 ± 42 interv: 168 ± 38
Ottens 2015 (13)	Netherlands	18	89	69 (56 - 73)	84 (76 - 97)	isolated CABG	NR	control: 73 (68 - 90) interv:51 (34 - 83)	control: 95 (81 - 105) interv: 66 (53 - 99)
Shalaby 2011 (11)	Finland	16	63	NR	NR	isolated CABG	NR	NR	NR
Toft 1997 (16)	Denmark	16	88	64 (57 - 70)	79 (73 - 84)	cardiac surgery	control: 165.0 ± 12 interv: 219.4 ±13 #	control: 43.8 ± 4 interv: 54.1 ± 9	control: 77.0 ± 6 interv: 113.1 ± 10 #
von Spiegel 2002 (14)	Germany	20	75	65 (53 - 72)	78 (61 - 97)	isolated CABG	NR	control: 65 ± 25 interv: 67 ± 28	control: 101 ± 34 interv: 103 ± 39

Data are presented as number, frequency, median ± standard deviation or median (full range). CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; Interv = intervention group; NR = not reported; Ref = reference. # $p < 0.05$ control versus intervention group.

Table 2. Characteristics and cardiopulmonary bypass protocols of included preclinical studies

Species	Animals (number)	Studies (number)	Body Weight (kg)	CPB time (hours)	Dilution (%)	Priming volume (mL)	Type of priming solution (number of studies)	Reference
Dog	165	10	10 – 34	1 – 2.75	17 – 25	500 – 1500	Crystalloid (8), donor blood (1), NR (1)	19, 40, 44, 45, 46, 47, 50, 51, 52, 35
Pig	292	15	6 – 67	1 – 3.75	15 – 25	350 – 1200	Crystalloid (5), donor blood and crystalloid (7), NR (3)	17, 18, 21-23, 25-28, 30, 31, 34, 43, 49, 53
Rabbit	43	2	2 – 4	1 – 1.5	18 – 20	570 – 600	Donor blood and crystalloid (1), NR (1)	24, 29
Rat	670	8	0.24 – 0.58	1 – 1.5	28 – 48	8 – 12	Crystalloid (2), colloid (6)	36-42, 54
Sheep	43	3	18 – 32	1.5 - 2	10 – 20	700 – 1000	Crystalloid (2), donor blood and crystalloid (1)	20, 32, 48

Data are presented as number or full range. CPB = cardiopulmonary bypass; NR = not reported.

CLINICAL EDEMA ASSESSMENT AND OUTCOME

Due to high heterogeneity between end points and measurement techniques used in clinical studies, a meta-analysis was considered unfeasible. A summary of the main findings per type of intervention is presented in Supplement 7 - Table 3. Most clinical studies[12-16] (*n*=5, 83%) used steroids as therapeutic agent of which three studies[12,14,16] (60%) observed a reduction in postoperative fluid gain, and one study[15] (20%) observed a reduction in glycocalyx shedding compared to control groups. In contrast, one study[13] (20%) observed no differences in cerebral edema following CPB. Apart from steroid administration, one study[11] (17%) investigated the effect of an aquaporin channel opener and observed no effect on postoperative myocardial edema formation.

PRECLINICAL EDEMA ASSESSMENT AND OUTCOME

We grouped the interventions based on general mechanism of action in the following groups: neutrophil inhibitors, modulators of coagulation, anti-inflammatory agents, complement inhibitors, antioxidants, matrix metalloproteinase inhibitors, modulators of endothelial barrier function, and vasoactive agents. Outcomes of all studies were summarized in Supplement 8 - Table 4 and details on administration protocols were summarized in Supplement 9 - Table 5. A total of 31 different drugs were tested of which 20 drugs (65%) reduced edema formation in at least one organ compared to untreated controls. Edema was quantified in 9 different organs; lung (*n*=20), kidney (*n*=3), heart (*n*=8), intestine (*n*=4), brain (*n*=5), skin (*n*=1), muscle (*n*=1), liver (*n*=1), and pancreas (*n*=1). A total of 31 different drugs were tested of which 20 drugs (65%) reduced edema formation in at least one organ compared to untreated controls.

PULMONARY EDEMA

CPB-associated pulmonary edema was reported in 20 studies, quantified as either lung water content[17,20-22,25-27,29,32,34,35,37,38,40-42,49] (Figure 2A) or extravasation of an albumin bound dye[33,36,39,54] (Figure 2B). In 16 out of these 20 studies (80%), administration of a preventive pharmacological agent reduced pulmonary edema (Supplement 8 - Table 4). A total of 18 different drugs were tested. Neutrophil inhibitors (SMD: -2.77 (95% CI -3.93 to -1.61), Figure 2A) and modulators of endothelial barrier (SMD: -2.33 (95% CI -4.69 to 0.03), Figure 2B) were particularly effective in reducing pulmonary edema following CPB compared to no treatment.

A

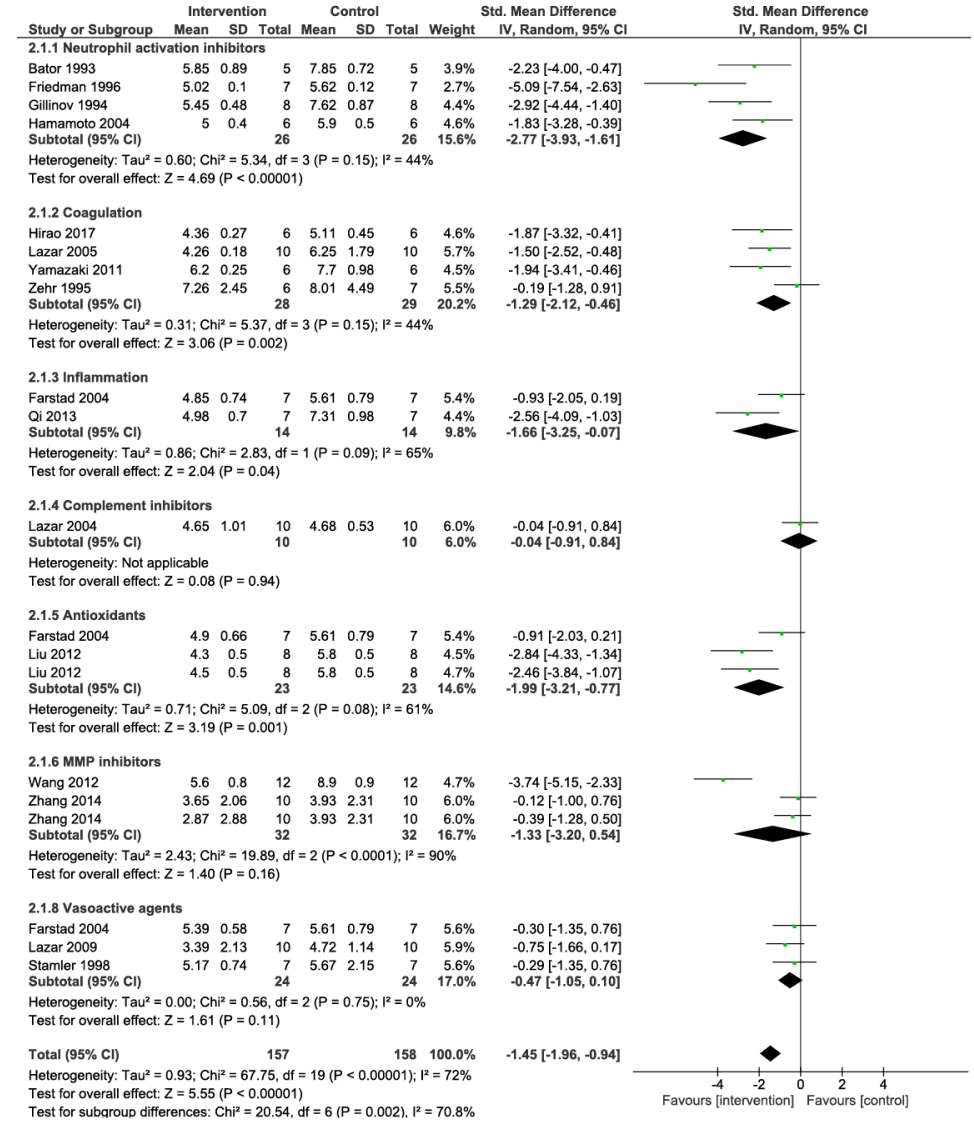

Figure 2. Pulmonary edema.

The effect of pharmacological agents on pulmonary edema following CPB in experimental models. Estimated differences in mean pulmonary wet-to-dry weight ratio (**A**) and tracer leakage (**B**) and accompanying 95% confidence intervals. Studies were weighted by the inverse of their variance; the area of each symbol is proportional to the weight of the study. The diamond represents the pooled effect.

B

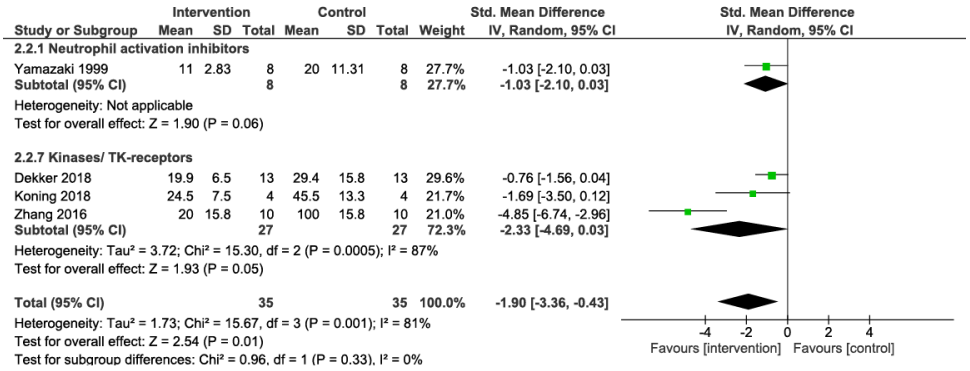

Figure 2. Continued

RENAL EDEMA

Renal edema was reported in 9% of the animal studies (Supplement 8 - Table 4). These three studies[36,39,49] tested 5 different pharmacological agents. Combined analysis favored the use of pharmacological agents that modulated endothelial barrier (SMD: -0.91 (95% CI -1.65 to -0.18), Figure 3A+B) to reduce renal edema following CPB compared to no treatment.

A

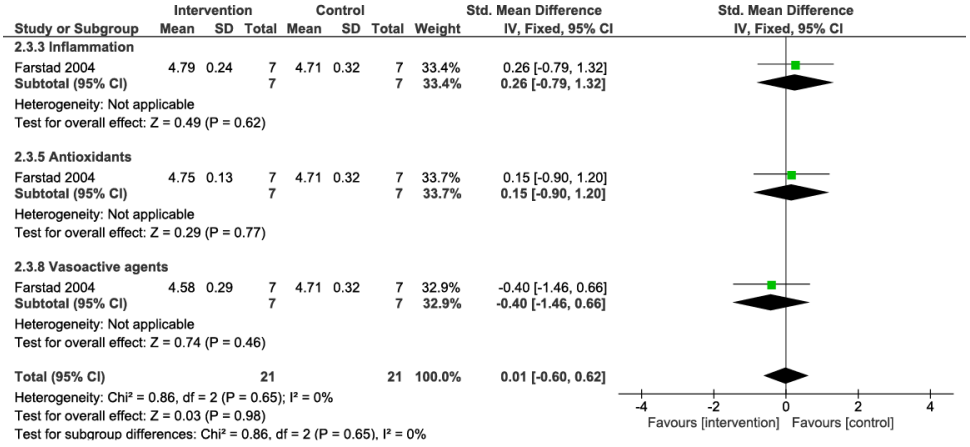

Figure 3. Renal edema

The effect of pharmacological agents on renal edema following CPB in experimental models. Estimated differences in mean renal wet-to-dry weight ratio (**A**) and tracer leakage (**B**) and accompanying 95% confidence intervals. Studies were weighted by the inverse of their variance; the area of each symbol is proportional to the weight of the study. The diamond represents the pooled effect.

B

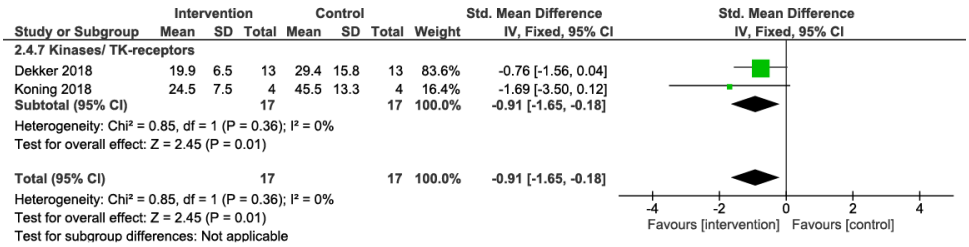

Figure 3. Continued

MYOCARDIAL EDEMA

Myocardial edema was reported in 8 animal studies (21%). Of these 8 studies, 4 studies[23,46,48,51] (50%) found a reduction in myocardial edema following CPB in the intervention group compared to no treatment (Supplement 8 - Table 4). Two studies[50,52] (25%) found no difference in total myocardial water gain after CPB, however faster edema resolution was observed in both intervention groups compared to no treatment. The antifibrinolytic agent aprotinin[23] was particularly effective in reducing myocardial edema (SMD: -2.05 (95% CI -3.43 to -0.67), Supplement 10 - Figure 4A+B).

INTESTINAL EDEMA

Intestinal edema was reported in 4 animal studies[39,49,53,55] (11%) in which 6 different drugs were tested (Supplement 8 - Table 4). Only one study[39] (25%) reported a reduction in CPB-induced intestinal edema (SMD: -1.98 (95% CI -3.92 to -0.04); Supplement 11 - Figure 5B). Overall however, administration of a pharmacological agent worsened intestinal edema following CPB compared to no treatment (SMD: 0.78 (95% CI 0.25 to 1.31); Supplement 11 - Figure 5A).

CEREBRAL EDEMA

Cerebral edema was reported in 5 animal studies (13%). Three studies[18,30,31] (60%) reported a reduction in cerebral edema formation following CPB in the intervention group compared to control CPB (Supplement 8 - Table 4). In contrast, two studies investigating the effect of anti-inflammatory drugs found no effect on post-CPB cerebral architecture[43] or water content.[24]

DISCUSSION

Preclinical evidence revealed that the administration of neutrophil inhibitors and direct modulators of endothelial barrier before onset of cardiopulmonary bypass (CPB) appear to be the most effective in reducing postoperative edema. Moreover, vulnerability to CPB-associated edema formation was organ-specific, as well as the response to preventive pharmacological agents. In particular, CPB-associated pulmonary edema reduced following most pharmacological agents, whereas the effect of these agents varied in other organs. The evidence for this finding comes from 32 preclinical studies, all investigating different types of potential leakage-preventing pharmacological agents in which the effect was determined in a variety of organs. Limited and heterogeneous data from clinical trials hampered analysis of clinical data.

Neutrophil inhibitors – Contact of blood with the artificial CPB surface causes activation of complement leading to activation and sequestration of neutrophils in tissues. Subsequent release of elastase and myeloperoxidase results in tissue edema and damage, which is most profoundly observed in the lungs.[2,17] The lungs receive all circulating neutrophils and due to the smaller diameter of pulmonary capillaries compared to systemic capillaries, this results in preferential trapping of neutrophils compared to other organs.[2] In line with this, prevention of neutrophil activation and adhesion via inhibition of Mac-1, was found effective in reducing pulmonary edema and neutrophil infiltration[17,20,22,33,37], however, not in myocardial[52] and intestinal tissue.[44] Inhibition of neutrophils using therapeutic agents or depletion of activated neutrophils using leukocyte filters[55-57] may therefore particularly reduce pulmonary damage and edema following CPB compared to other organs, even though complement activation itself remains unaffected.

Modulators of endothelial barrier function – Recent studies[36,39,54] investigated the effect of agents that directly modulate molecular systems involved in endothelial barrier regulation. Activation of endothelial tyrosine-protein kinase receptor 2 (Tie2)[36] or inhibition of Src kinase[54] were associated with reduced pulmonary edema. Moreover, the administration of Imatinib, a bcr/abl tyrosine kinase inhibitor, reduced pulmonary, intestinal and renal edema and injury following CPB.[39] The success of these interventions may result from the fact that modulation of endothelial receptors or downstream effectors can promote a wide range of vascular stabilizing effects, such as downregulation of adhesion molecule expression, reorganization

of the actin cytoskeleton and accumulation of VE-cadherin at endothelial junctions. Moreover, instead of attenuating the action of circulating neutrophils or inflammatory molecules, these strategies are directly targeted at the desired site of action, namely the vascular endothelium. Thus, interventions directly targeted at endothelial barrier function appear one of the most promising strategies to reduce edema formation in multiple vital organs following CPB.

Complement system inhibitors – Complement activation during CPB results from the exposure of blood to the artificial surface of the CPB system. This contributes to inflammatory injury mainly through generation of pro-inflammatory mediators and activation and transmigration of neutrophils. Biocompatible coatings and miniaturization of bypass circuits have therefore been introduced to reduce complement activation from the exposure of blood to the surface of the bypass system.[58] In addition, pharmacological interventions such as direct inhibitors of complement[53] or the administration of soluble complement receptor type 1 (sCR1)[21,25], have demonstrated some benefit on myocardial function and mortality in selected subgroups of patients following CPB. Interestingly, none of the animal studies observed any effect of sCR1 administration or inhibition of C5a on postoperative edema.[21,25,53] Inhibition of complement at an earlier stage and at multiple levels may potentially be more successful in reducing myocardial injury[59,60], however the effect on postoperative edema following CPB remains uncertain.

Anti-inflammatory agents – CPB induces a systemic inflammatory reaction that involves increased permeability of the vascular endothelium. Intuitively, given the association between increased levels of pro-inflammatory cytokines (e.g. interleukin-6) and outcome following CPB[61,62], attenuation of systemic inflammation using steroids was proposed as one of the first strategies to reduce postoperative edema and organ dysfunction. However, the evidence to support their use remains controversial, as multiple large trials fail to show clear clinical benefits.[63-65] Similarly, preventive administration of methylprednisolone failed to reduce postoperative edema in most preclinical studies.[24,28,49] Recent clinical trials further focused on extra-corporeal removal of cytokines using hemoadsorption devices to suppress inflammation. However, the use of these devices during CPB so far also failed to improve postoperative outcome.[66-68] As complement activation persists, treatment strategies primarily focused on reducing systemic inflammation may not be sufficient to entirely preserve endothelial function and adequately reduce postoperative edema and preserve organ function.

Modulators of coagulation – Despite systemic heparinization, thrombin is generated during CPB. Aside from its role as effector protease of the coagulation cascade, thrombin is known to increase endothelial permeability via activation of protease-activated receptor 1 (PAR1) on the vascular endothelium.[69] Modulation of PAR1 signaling using either thrombomodulin[38], activated protein C[42], or aprotinin[23,27] improved both hemostasis and endothelial barrier function following CPB. These agents preserved endothelial adherens junction structure[23], reduced neutrophil infiltration[27], and improved vasomotor tone[18,19] in a variety of organs. Collectively, agents modulating PAR1 may potentially provide unique treatment strategies to balance both coagulation and inflammatory systems during CPB.

Matrix metalloproteinase inhibitors – Onset of CPB causes the release of matrix metalloproteinases (MMPs). These are proteolytic enzymes that are known to degrade basement membrane and extracellular matrix, which are essential for inflammatory associated neutrophil extravasation and infiltration. Inhibitors of MMPs were therefore proposed as strategy to reduce CPB-associated neutrophil infiltration and subsequent organ injury. Interestingly, in addition to their anti-microbial activity, tetracyclines are thought to have both anti-apoptotic and anti-inflammatory effects via attenuation of both tumor necrosis factor alpha (TNFα) and via reduction of neutrophil infiltration through inhibition of MMPs. Indeed, preclinical evidence suggest that tetracyclines reduce cerebral[30] and pulmonary[35,41] injury and edema formation, however, this organ protective effect could not be confirmed in a recent clinical trial, despite confirming reduced MMP activity.[70]

Antioxidants – Particularly during the early reperfusion phase during CPB, excessive amounts of oxygen free radicals are generated leading to cellular damage. Propofol anesthesia and the use of modified closed and miniaturized CPB have been reported to reduce the reactive oxygen species (ROS) burst.[71] Moreover, the administration agents with antioxidant properties are thought to additionally inhibit neutrophil aggregation[71] and to counteract the negative interstitial fluid hydrostatic pressure thereby reducing edema.[72,73] However, available preclinical data remains conflicting[30,40,49,50] and further research is needed to clarify whether antioxidants may have a role in reducing postoperative edema.

Vasoactive agents – Conflicting results were reported concerning strategies that either enhanced water excretion or vasodilation to reduce organ injury following.[26,32,45-49,51] Although these agents may reduce myocardial ischemia reperfusion injury[46,48,51],

available data remain inconclusive relating its effect on edema formation following CPB. This is in line with recent insights that there appears to be a loss of hemodynamic coherence in systemic inflammatory conditions, meaning that optimization of systemic vascular resistance and macrocirculatory parameters may not necessarily lead to improvement of microvascular function.[74]

LIMITATIONS

This review has some limitations. First, meta-analyses are based on preclinical data only. These studies were performed in a range from small to large animals in which different CPB models, bypass times and follow-up periods were studied. Also, these studies were conducted over a period of 37 years. This has contributed to observed heterogeneity. As most of the animal studies did not report power calculations in their methodology, did not use randomization of treatment or study groups, and did not have blinded outcome assessment, external validity of the preclinical findings in humans may be questioned. However, data were obtained from a large number of studies in which edema was mostly defined as one of the primary outcomes of the studies, which strengthen our findings. Lastly, possible improvements in CPB techniques were beyond the scope of this review.

CONCLUSION

Increased vascular permeability and edema following cardiac surgery with CPB is an often observed complication contributing to postoperative organ dysfunction. The pathophysiology is complex and involves the activation of blood components and the transition of the endothelium to a more leaky phenotype (Figure 4). Overall, neutrophil inhibition and direct modulators of endothelial barrier appear most effective in reducing edema formation, in particular pulmonary edema, in experimental models of CPB. However, due to the complex pathophysiology and organ specific responses, future research should focus on a combination of strategies targeting neutrophil infiltration and preventive strengthening of the vascular endothelial barrier to effectively reduce postoperative edema in all organs. Moreover, future research should increase follow-up times to clarify the effects of these agents on organ function and outcome following CPB.

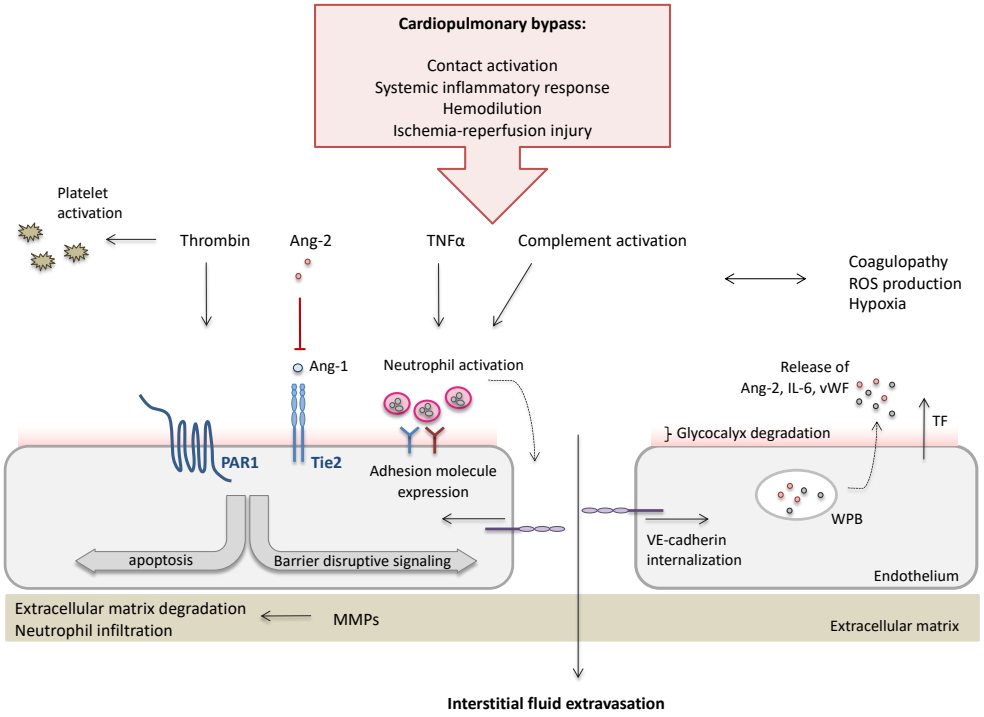

Figure 4. Summary of main findings concerning molecular pathways involved in cardiopulmonary bypass associated endothelial barrier dysfunction and subsequent edema formation. Onset of cardiopulmonary bypass is associated with contact activation, hemodilution and a systemic inflammatory response, resulting in the release of pro-inflammatory mediators (such as TNFα and IL-6) and shedding of endothelial glycocalyx components. Upon inflammatory activation, endothelial adhesion molecule expression (e.g. VCAM-1, P-sel) and neutrophil activation and transmigration is stimulated. Moreover, angiopoietin-2 (Ang-2) is released from endothelial Weibel-Palade bodies (WPB) and prevents angiopoietin-1 (Ang-1) from Tie2 binding. In addition, thrombin is excessively generated resulting in activation of coagulation and endothelial protease-activated receptor-1 (PAR1). Collectively, this results in internalization of VE-cadherins and activation of cell contraction leading to increased endothelial permeability and tissue edema. *ICAM-1, intercellular adhesion molecule 1; MMP, matrix metalloproteinase; P-sel, P-selectin; ROS, reactive oxygen species; TF, tissue factor; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand Factor; TNFα, tumor necrosis factor alpha.*

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SUPPLEMENTAL DATA

Appendix A – Supplemental methods Full search strategy
Appendix B – Supplemental data
Supplement 1 – PRISMA checklist
Supplement 2 – Table 1 Quality assessment of Individual clinical studies
Supplement 3 – Table 2 Quality assessment of individual preclinical studies
Supplement 4 – Figure 1 Summary of quality assessment of included clinical studies
Supplement 5 – Figure 2 Summary of quality assessment of included preclinical studies
Supplement 6 – Figure 3 Funnel plot pulmonary edema
Supplement 7 – Table 3 Outcome of clinical studies per type of intervention
Supplement 8 – Table 4 Outcome of preclinical studies per type of intervention
Supplement 9 – Table 5 Details of treatment strategies of preclinical studies
Supplement 10 – Figure 4A+B Meta-analysis for myocardial edema
Supplement 11 – Figure 5A+B Meta-analysis for intestinal edema

SUPPLEMENTAL METHODS

PUBMED SEARCH

First search (15-08-2018): 878 items; Re-run search (19-03-2019): 20 new items.

("Cardiopulmonary Bypass"[Mesh] OR cardiopulmonary bypass*[tiab] OR cardio-pulmonary bypass*[tiab] OR CPB[tiab] OR heart bypass*[tiab]) AND ("Pulmonary Edema"[Mesh] OR "Brain Edema"[Mesh] OR "Edema, Cardiac"[Mesh] OR edema[tiab] OR oedema[tiab] OR capillary leak*[tiab] OR vascular leak*[tiab] OR microvascular leak*[tiab] OR "Capillary Permeability"[Mesh] OR "Capillary Leak Syndrome"[Mesh] OR capillary permeab*[tiab] OR vascular permeab*[tiab] OR microvascular permeab*[tiab] OR capillary barrier*[tiab] OR vascular barrier*[tiab] OR microvascular barrier*[tiab] OR fluid extravasation[tiab] OR "Glycocalyx"[Mesh] OR Glycocalyx[tiab] OR capillary hyperpermeab*[tiab] OR vascular hyperpermeab*[tiab] OR microvascular hyperpermeab*[tiab] OR capillary hyper-permeab*[tiab] OR vascular hyper-permeab*[tiab] OR microvascular hyper-permeab*[tiab] OR "Capillary Fragility"[Mesh] OR capillary fragility[tiab] OR endothelial fragility[tiab] OR vascular fragility[tiab] OR microvascular fragility[tiab])

EMBASE.COM SEARCH

First search (15-08-2018): 1617 items; Re-run search (19-03-2019): 45 new items.

('cardiopulmonary bypass'/exp OR 'cardiopulmonary bypass*':ab,ti,kw OR 'cardio-pulmonary bypass*':ab,ti,kw OR cpb:ab,ti,kw OR 'heart bypass*':ab,ti,kw) AND ('vascular leakage'/exp OR 'lung edema'/exp OR 'brain edema'/exp OR 'heart edema'/exp OR edema:ab,ti,kw OR oedema:ab,ti,kw OR 'capillary leak*':ab,ti,kw OR 'vascular leak*':ab,ti,kw OR 'microvascular leak*':ab,ti,kw OR 'capillary permeability'/exp OR 'capillary leak syndrome'/exp OR 'capillary permeab*':ab,ti,kw OR 'vascular permeab*':ab,ti,kw OR 'microvascular permeab*':ab,ti,kw OR 'capillary barrier*':ab,ti,kw OR 'vascular barrier*':ab,ti,kw OR 'microvascular barrier*':ab,ti,kw OR 'fluid extravasation':ab,ti,kw OR 'glycocalyx'/exp OR glycocalyx:ab,ti,kw OR 'capillary hyperpermeab*':ab,ti,kw OR 'vascular hyperpermeab*':ab,ti,kw OR 'microvascular hyperpermeab*':ab,ti,kw OR 'capillary hyper-permeab*':ab,ti,kw OR 'vascular hyper-permeab*':ab,ti,kw OR 'microvascular hyper-permeab*':ab,ti,kw OR 'vascular fragility'/exp OR 'capillary fragility':ab,ti,kw OR 'endothelial fragility':ab,ti,kw OR 'vascular fragility':ab,ti,kw OR 'microvascular fragility':ab,ti,kw)

COCHRANE LIBRARY SEARCH

First search (15-08-2018): 97 items (trials); Re-run search (19-03-2019): 2 new items (trials).

((“cardiopulmonary bypass*” OR “cardio-pulmonary bypass*” OR CPB OR “heart bypass*”) AND (edema OR oedema OR “capillary leak*” OR “vascular leak*” OR “microvascular leak*” OR “capillary permeab*” OR “vascular permeab*” OR “microvascular permeab*” OR “capillary barrier*” OR “vascular barrier*” OR “microvascular barrier*” OR “fluid extravasation” OR Glycocalyx OR “Capillary hyperpermeab*” OR “vascular hyperpermeab*” OR “microvascular hyperpermeab*” OR “capillary hyper-permeab*” OR “vascular hyper-permeab*” OR “microvascular hyper-permeab*” OR “capillary fragility” OR “endothelial fragility” OR “vascular fragility” OR “microvascular fragility”)):ab,ti,kw

SUPPLEMENT 1

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (Suppl Methods)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7

Supplement 1. Continued

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 Table 1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 (Suppl. 2-5)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11 (Fig 2-3, Suppl. 10-11)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11 (Fig 2-3, Suppl. 10-11)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 (Suppl. 6)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15 (Fig. 4)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15-16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENT 2

Table 1. Quality assessment of individual clinical studies

	1. Study described as randomized?	2. Adequate randomization?	3. Concealment of allocation	4. Care givers / providers blinded?	5. Outcome assessors blinded?	6. Groups similar at baseline?	7. Overall drop out < 20%?	8. Differential drop out < 15%?	9. High adherence to treatment?	10. Other interventions avoided or similar?	11. Outcome measured with valid tools?	12. Sufficient sample size?	13. Outcomes or sub analysis prespecified?	Randomization at any point?	Blinding at any point?
Brettner 2018	Yes	CD	CD	Yes	Yes	Yes	CD	CD	Yes	Yes	Yes	NR	Yes	**Unclear**	**Yes**
Miranda 1982	Yes	Yes	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	NR	Yes	**Yes**	**Yes**
Ottens 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	**Yes**	**Yes**
Shalaby 2011	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	**Unclear**	**Yes**
Toft 1997	Yes	NR	NR	NR	NR	Yes	Yes	Yes	Yes	Yes	CD	NR	Yes	**Unclear**	**Unclear**
Von Spiegel 2002	Yes	NR	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**Unclear**	**Yes**

Quality assessment based on NIH quality assessment of clinical intervention studies. "Yes", "Unclear", "No" indicates "low", "unclear", and "high" risk of bias, respectively. CD = cannot determine, NR = not reported.

SUPPLEMENT 3

Table 2. Quality assessment of individual preclinical studies

	1. Randomization group allocation?	2. Groups similar at baseline?	3. Concealment of allocation?	4. Random housing?	5. Care givers / investigators blinded?	6. Random selection outcome	7. Outcome assessors blinded?	8. Incomplete outcome data addressed?	9. Free of selective outcome reporting?	11. Drug tested in sham group?	12. Power calculation?	13. Ethical approval?	Randomization at any point?	Blinding at any point?
Bator 1993	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Ben Mime 2005	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Cox 2000	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**No**
Cox 2003	No	Yes	No	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Cox 2002	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Cox 2009	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Dekker 2018	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	**Yes**	**No**
Egan 2009	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	**Yes**	**Yes**
Farstad 2004	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Fessatidis 1994	Unclear	Yes	Unclear	Unclear	No	Unclear	Yes	Unclear	Yes	No	No	Unclear	**No**	**Yes**
Fischer 2003	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Flameng 1981	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Unclear	**No**	**No**
Friedman 1996	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear	No	No	No	Yes	**No**	**No**
Gillinov 1993	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes	**No**	**Yes**
Gillinov 1994	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**No**
Hagl 2001	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	**Yes**	**Yes**
Hamamoto 2004	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	No	No	Yes	**No**	**No**

Hirao 2017	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	Yes	No	No	Yes	**Yes**	**Yes**
Khan 2005	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**No**
Kim 1999	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Unclear	No	No	No	Yes	**Yes**	**No**
Koning 2018	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Yes	Yes	**Yes**	**No**
Lazar 2004	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	No	No	No	Yes	**Yes**	**No**
Lazar 2009	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	No	No	Yes	**Yes**	**Yes**
Lazar 2005	Yes	Yes	Yes	Unclear	No	Unclear	Unclear	Yes	Yes	No	No	Yes	**Yes**	**No**
Liu 2012	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	**Yes**	**Yes**
Mühlfeld 2008	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**No**
Qi 2013	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	No	No	No	Yes	**Yes**	**No**
Salameh 2015	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Unclear	Yes	Yes	No	Yes	**Yes**	**Yes**
Shum-Tim 2001	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	No	No	Yes	**Yes**	**Yes**
Sauer 2001	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	No	Yes	**No**	**No**
Stamler 1998	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**Yes**
Tofukuji 2000	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**No**	**No**
Wang 2012	Yes	Unclear	Yes	Yes	No	Unclear	Unclear	Unclear	No	No	No	Yes	**Yes**	**No**
Yamazaki 2011	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	**Yes**	**No**
Yamazaki 1999	Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	No	No	No	Yes	**No**	**No**
Zehr 1995	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	No	Yes	**No**	**Yes**
Zhang 2014	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Unclear	No	No	No	Yes	**Yes**	**No**
Zhang 2016	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	No	No	No	No	Yes	**Yes**	**No**

Quality assessment based on SYRCLE Risk of Bias tool. “Yes”, “Unclear”, “No” indicates “low”, “unclear”, and “high” risk of bias, respectively.

SUPPLEMENT 4

Figure 1. Summary of quality assessment of included clinical studies.

SUPPLEMENT 5

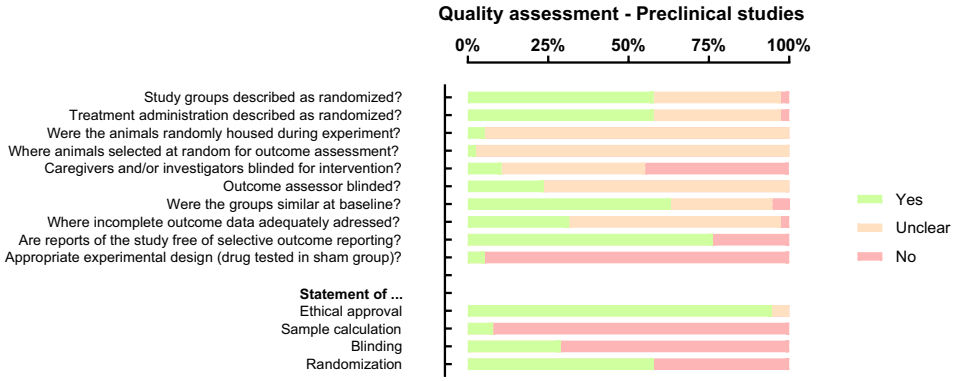


Figure 2. Summary of quality assessment of included preclinical studies.

SUPPLEMENT 6

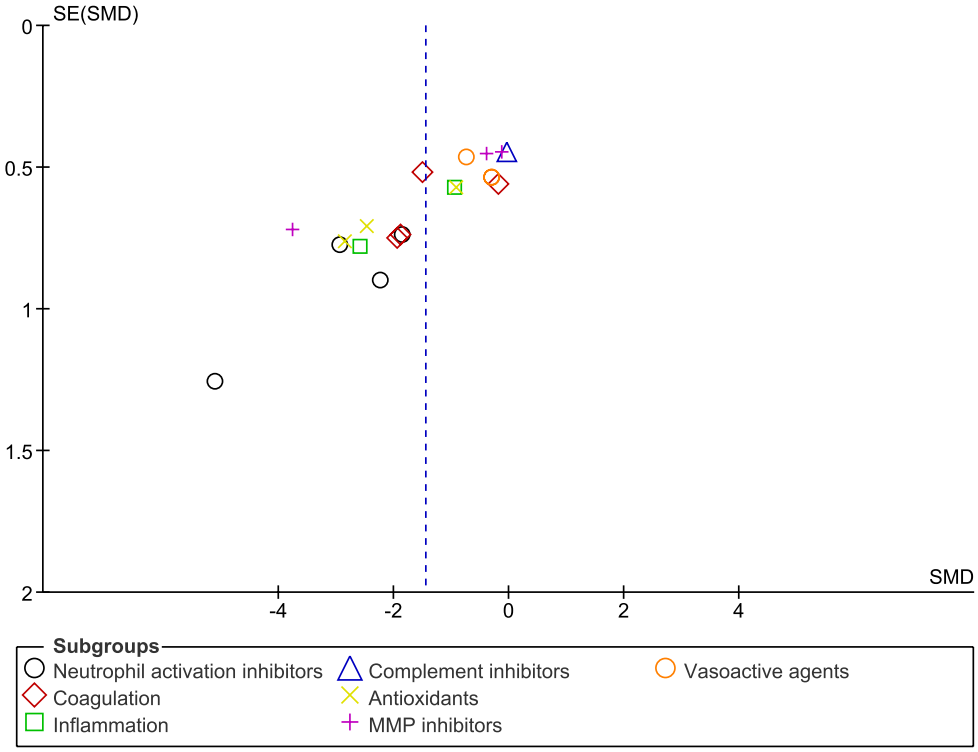


Figure 3. Funnel plot for pulmonary edema

SUPPLEMENT 7

Table 3. Outcome of clinical studies per type of intervention

Type of intervention	Drug	Concentration	Follow-up	Organ	Measurement/ technique	Outcome	Reference
Anti-inflammatory agents	Hydrocortisone	10 mg	4 h	Total body	Plasma heparan-sulphate levels	Reduction glycocalyx shedding	Brettner 2018
	Dexamethasone	1 mg / kg	15 h	Total body	Fluid balance	Reduction fluid gain	Miranda 1982
	Dexamethasone	1 mg / kg	0 h	Brain	MRI	No effect	Ottens 2015
	Methylprednisolone	30 mg / kg	24 h	Total body	Fluid balance	Reduction fluid gain	Toft 1997
	Dexamethasone	1 mg / kg	20 h	Lung	Extravascular water content	Reduction edema	Von Spiegel 2002
Other	Diazoxide	50 ug / L	0 h	Heart	Histology	No effect	Shalaby 2011

H = hour(s).

SUPPLEMENT 8

Table 4 Outcome of preclinical studies per type of intervention

Type of intervention	Drug	Animal	Follow-up	Organ	Measurement	Outcome	Reference
Neutrophil	NPC 15669	pig	2 h	Lung	Tissue water content	Prevention edema	Bator 1993
inhibitors	NPC 15669	sheep	1 h	Lung	Tissue water content	Reduction edema	Friedman 1996
	NPC 15669	pig	2 h	Lung	Tissue water content	Reduction edema	Gillinov 1994
	TBC 1269	dog	30 min	Intestine	Tissue water content	No effect on total edema, however faster edema resolution	Cox 2000
	TBC 1269	dog	2 h	Heart	Tissue water content	No effect on total edema, however faster edema resolution	Sauer 2001
	ONO-5046-Na	dog	5 h	Lung	Tissue water content	Reduction edema	Yamazaki 1999
	Rolipram	rats	1 h	Lung	Tissue water content	Prevention edema	Hamamoto 2004
Modulators of	Eptifibatide	pig	30 min	Brain	FITC-dextran extravasation	Reduction leakage	Ben Mime 2005
coagulation	Prostacyclin (PGI2)	dog	30 min	Lung	Histological examination	Prevention of structural changes	Fessatidis 1994
	SDZ HUL-412	pig	2 h	Lung	Tissue water content	No effect	Zehr 1995
	Recombinant soluble Thrombomodulin	rat	4 h	Lung	Tissue water content	Reduction edema	Hirao 2017
	Activated protein C (APC)	rat	1 h	Lung	Tissue water content	Reduction edema	Yamazaki 2011
	Aprotinin	pig	1 h 30 min	Heart	Tissue water content	Reduction edema	Khan 2005
	Aprotinin	pig	0 min	Lung	Tissue water content	Reduction edema	Lazar 2005
Anti-inflammatory agents	Methylprednisolone	pig	0 min	Lung, kidney, heart, intestine	Tissue water content	No effect	Farstad 2004

	Methylprednisolone	rabbit	10 min	Brain	Tissue water content	No effect	Kim 1999
	Methylprednisolone	pig	8 h	Lung	Histological examination	No effect	Muhlfeldt 2008
	Methylprednisolone	pig	6 h	Total body Brain	Total body weight Trypan blye extravasation	Reduction weight gain Reduction cerebral leakage	Shum-Tim 2001
	Cyclosporine A	pig	7 days	Brain	Histological examination	No effect	Hagl 2001
	Anti-TNF alpha antibody (TNFa-Ab)	rabbit	0 min	Lung	Tissue water content	Prevention edema	Qi 2013
Complement system inhibitors	Soluble complement receptor-1 (sCR1)	pig	2 h	Lung	Histological examination	No effect	Gillinov 1993
	Soluble complement receptor-1 (sCR1)	pig	0 min	Lung	Tissue water content	No effect	Lazar 2004
	C5a monoclonal antibody (C5a Mab)	pig	2 h	Intestine	Tissue water content	No effect	Tofukuji 2000
Antioxidants	Vitamin-C	pig	0 min	Lung, kidney, heart, intestine	Tissue water content	No effect	Farstad 2004
	N-acetylcysteine	dog	2 h	Heart	Tissue water content	No effect on total edema, however faster edema resolution	Fischer 2003
	Curcumin Low-dose (L-Cur)	rat	24 h	Lung	Tissue water content	Reduction edema	Liu 2012
	Curcumin High-dose (H-Cur)	rat	24 h	Lung	Tissue water content	Reduction edema	Liu 2012
	Epigallocatechin-3-gallate (EGCG)	pig	2 h	Brain	Histological examination	Reduction structural changes	Salameh 2015
Matrix metalloproteinase inhibitors	Minocycline	pig	2 h	Brain	Histological examination	Prevention edema	Salameh 2015
	Doxycycline	rat	6 h	Lung	Tissue water content	Reduction edema	Wang 2012

Table 4 Continued

	Doxycycline Low-dose	dog	3 h	Lung	Tissue water content	Reduction edema	Zhang 2014
	Doxycycline High-dose	dog	3 h	Lung	Tissue water content	No effect	Zhang 2014
Modulators of endothelial barrier receptors and kinases	Vasculotide	rat	1 h	Lung, kidney	Evans Blue dye extravasation	Reduction pulmonary leakage, not in kidneys	Dekker 2018
	Imatinib	rat	1 h	Lung, kidney, intestine	Evans Blue dye extravasation	Reduction pulmonary and intestinal leakage, not in kidneys	Koning 2018
	PP2	rat	24 h	Lung	Evans Blue dye extravasation	Reduction leakage	Zhang 2016
Vasoactive agents	Nesitride	pig	0 min	Lung	Tissue water content	No effect	Lazar 2009
	Alpha-trinositol	pig	0 min	Lung, kidney, heart, intestine	Tissue water content	No effect	Farstad 2004
	Dopexamine	sheep	2 h	Lung	Tissue water content	No effect	Stamler 1998
Other	EMD 87580	dog	2 h	Heart	Tissue water content	No effect	Cox 2003
	EMD 96 785	dog	2 h	Heart	Tissue water content	Reduction edema	Cox 2002
	EMD 96 785	dog	2 h	Heart	Tissue water content	No effect	Cox 2009
	Poloxamer 188	sheep	9 h	Heart	Evans Blue dye extravasation	Reduction leakage	Egan 2009
	Lidoflazine	dog	30 min	Heart	Histological examination	Prevention edema	Flameng 1981

H = hour(s); min = minutes.

SUPPLEMENT 9

Table 5. Details of treatment strategies of preclinical studies

Type of intervention	Drug	Control	Route	Loading dose	Additional dose	Continuous infusion	Reference
Neutrophil inhibitors	NPC 15669	vehicle	iv	10 mg / kg	-	6 mg / kg /h	Bator 1993
	NPC 15669	no treatment	iv	10 mg / kg	-	6 mg / kg / h	Friedman 1996
	NPC 15669	vehicle	iv	10 mg / kg	10 mg / kg (during CPB)	6 mg / kg /h	Gillinov 1994
	TBC 1269	vehicle	iv	25 mg / kg	-	5 mg / kg	Cox 2000
	TBC 1269	vehicle	iv	25 mg / kg	-	5 mg / kg / h	Sauer 2001
	ONO-5046-Na	no treatment	iv	15 mg / kg	-	15 mg / kg / h	Yamazaki 1999
	Rolipram	no treatment	iv	40 ug / kg	-	40 ug / kg / min	Hamamoto 2004
Modulators of coagulation	Eptifibatide	no treatment	iv	360 ug / kg	-	20 ug / kg / min	Ben Mime 2005
	Prostacyclin (PGI2)	no treatment	iv	10 ng / kg	-	20 ng / kg / min	Fessatidis 1994
	SDZ HUL-412	vehicle	iv	3 mg / kg	-	2 mg / kg / h	Zehr 1995
	recombinant soluble Thrombomodulin	no treatment	iv	3 mg / kg	-	-	Hirao 2017
	Activated protein C (APC)	vehicle	iv	0.1 mg / kg	-	-	Yamazaki 2011
	Aprotinin	vehicle	iv	40.000 KIU / kg	40.000 KIU / kg (during CPB)	10.000 KIU / kg / h	Khan 2005
	Aprotinin	no treatment	iv	40.000 KIU / kg	-	20.000 KIU / kg / h	Lazar 2005
Anti-inflammatory agents	Methylprednisolone	no treatment	im	2x 30 mg / kg	-	-	Farstad 2004
	Methylprednisolone	no treatment	iv	30 mg / kg	-	-	Kim 1999
	Methylprednisolone	saline	iv	30 mg / kg	-	-	Muhlfeldt 2008
	Methylprednisolone	similar in priming	iv	30 mg / kg	-	-	Shum-Tim 2001
	Cyclosporine A	vehicle	iv	2.5 mg / kg	2.5 mg / kg (post-CPB)	-	Hagl 2001

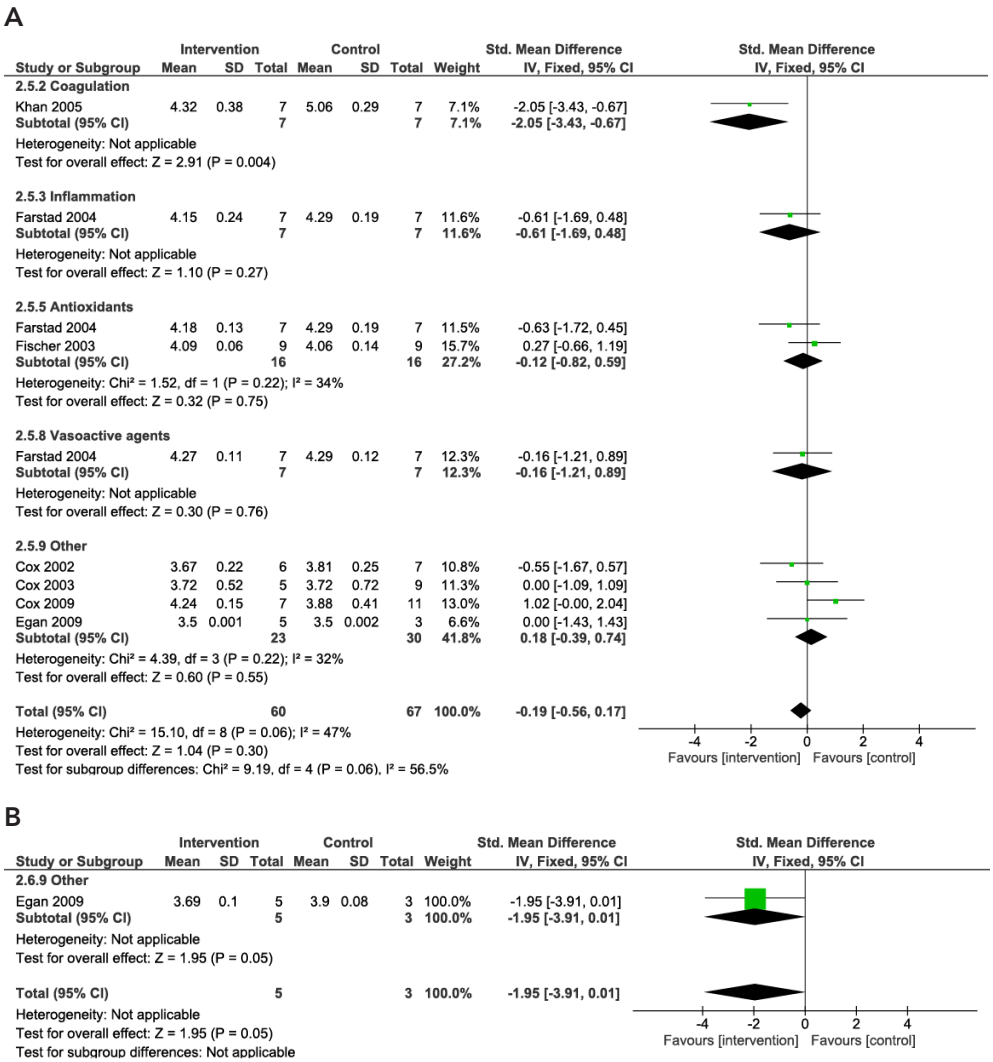
Table 5. Continued

	Anti-TNF alpha antibody (TNFa-Ab)	vehicle	oral	1200 pg / kg	1200 pg / kg (during CPB)	-	Qi 2013
Complement system inhibitors	Soluble complement receptor-1 (sCR1)	saline	iv	6 mg / kg	6 mg / kg (end-CPB)	-	Gillinov 1993
	Soluble complement receptor-1 (sCR1)	no treatment	iv	10 ml / kg	no	-	Lazar 2004
	C5a monoclonal antibody (C5a Mab)	vehicle	iv	1.6 mg / kg	no	-	Tofukuji 2000
Antioxidants	Vitamin-C	no treatment	iv	1000 mg	-	14 mg / kg / h	Farstad 2004
	N-acetylcyrsteine	vehicle	iv	100 mg / kg	-	20 mg / kg / h	Fischer 2003
	Curcumin Low-dose (L-Cur)	vehicle	ip	50 mg / ml	50 mg / ml (12 h post-CPB)	-	Liu 2012
	Curcumin High-dose (H-Cur)	vehicle	ip	200 mg / ml	200 mg / ml (12h post-CPB)	-	Liu 2012
	Epigallocatechin-3-gallate (EGCG)	no treatment	iv	10 mg / kg	10 mg / kg (post-CPB)	-	Salameh 2015
Matrix metalloproteinase inhibitors	Minocycline	no treatment		4 mg / kg	4 mg / kg (post-CPB)	-	Salameh 2015
	Doxycycline	no treatment	oral	7 x 30 mg kg / day	-	-	Wang 2012
	Doxycycline Low-dose	no treatment	oral	3x 30 mg / kg / day	-	-	Zhang 2014
	Doxycycline High-dose	no treatment	oral	3x 60 mg / kg / day	-	-	Zhang 2014
Modulators of endothelial	Vasculotide	vehicle	iv	200 ng	-	-	Dekker 2018

barrier receptors and kinases	Imatinib	vehicle	ip	ND	-	-	Koning 2018
	PP2	no treatment	ip	1 mg / kg	-	-	Zhang 2016
Vasoactive agents	Nesitride	vehicle	iv	2 ug / kg	-	0.01 ug / kg / min	Lazar 2009
	Alpha-trinositol	no treatment	iv	120 mg	-	40 mg / h	Farstad 2004
	Dopexamine	vehicle	iv	2 ug / kg / min	-	2 ug / kg / min	Stamler 1998
Other	EMD 87580	vehicle	iv	5 mg / kg	-	-	Cox 2003
	EMD 96 785	vehicle	iv	3 mg / kg	-	-	Cox 2002
	EMD 96 785	vehicle	iv	3 mg / kg	-	-	Cox 2009
	Poloxamer 188	vehicle	iv	2 mL / kg		0.2 mL / kg / min	Egan 2009
	Lidoflazine	vehicle	iv	1.25 mg / kg	-	-	Flameng 1981

Iv = intravenous; ip = intraperitoneal; im = intramuscular; KIU = kallikrein inhibitor unit.

SUPPLEMENT 10

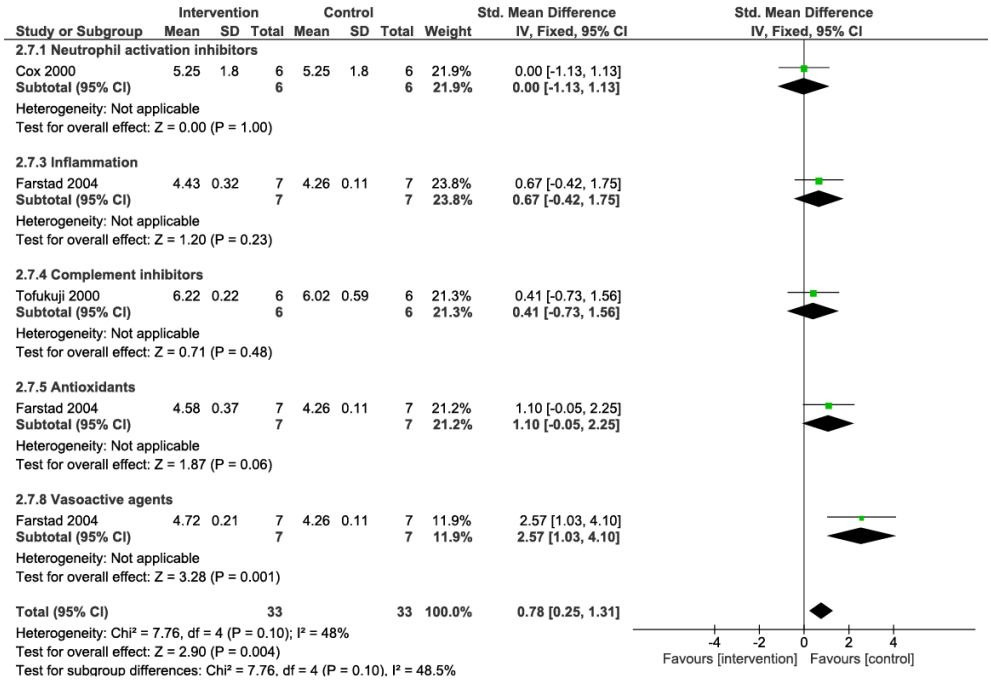


Supplemental Figure 4. Myocardial edema.

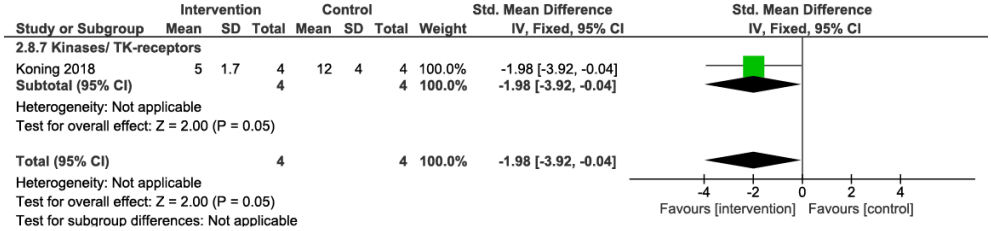
The effect of pharmacological agents on myocardial edema following CPB in experimental models. Estimated differences in mean myocardial wet-to-dry weight ratio (**A**) and tracer leakage (**B**) and accompanying 95% confidence intervals. Studies were weighted by the inverse of their variance; the area of each symbol is proportional to the weight of the study. The diamond represents the pooled effect.

SUPPLEMENT 11

A



B



Supplemental Figure 5. Intestinal edema.

The effect of pharmacological agents on intestinal edema following CPB in experimental models. Estimated differences in mean intestinal wet-to-dry weight ratio (**A**) and tracer leakage (**B**) and accompanying 95% confidence intervals. Studies were weighted by the inverse of their variance; the area of each symbol is proportional to the weight of the study. The diamond represents the pooled effect.